

Implications of Stage-Specific Survival Rates in Assessing Recent Declines in Prostate Cancer Mortality Rates

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It has been noted that the most important evidence for a benefit of early detection of prostate cancer using prostate-specific antigen (PSA) testing would be a decline in prostate cancer mortality rates to levels below those existing before diagnostic use of PSA testing. We document a decrease in U.S. prostate cancer mortality rates in white men less than 85 years of age to levels below those existing in 1986, the year use of PSA testing was approved. In fact, for men 60–79 years of age, prostate cancer mortality rates were lower in 1997 than in any

year since 1950. Although it has been argued that the decrease in prostate cancer mortality rates began too soon to be explained by PSA testing, stage-specific survival rates indicate that a rapid decrease in mortality may be explained by the large number of high-grade prostate cancers detected before metastasis. If recent decreases in U.S. prostate cancer mortality rates are due to early detection using PSA testing, randomized clinical trials investigating PSA testing will show early evidence of a mortality benefit. (Epidemiology 2000;11:167–170)

Keywords: mortality, prostate neoplasms, survival, time trends, tumor staging, race.

Gann¹ described the temporal pattern of cancer incidence and mortality rates that would provide evidence of the efficacy of a newly introduced screening method for cancer. Several reports have noted that the pattern of prostate cancer incidence in U.S. men is consistent with a beneficial effect of screening with prostate-specific antigen (PSA) testing, which was approved by the Food and Drug Administration for diagnostic uses in 1986. That is, total prostate cancer incidence rates increased sharply from 1987 through 1992 and decreased thereafter, and incidence rates for distant disease (ie, prostate cancer with distant metastases at the time of diagnosis) have been decreasing since at least 1991.^{2–11} A recent report indicates that the decrease in total prostate cancer incidence after 1992 is due, at least in part, to a reduction in the use of PSA testing in previously untested, cancer-free men.¹² Thus, the decrease in prostate cancer incidence after 1992 may not provide unequivocal evidence of a depletion of prevalent cases expected on the basis of Gann's paradigm.¹ As Gann noted, however, the ultimate and most important sign of a benefit of PSA testing would be a reduction of prostate cancer mortality rates to levels below those existing before diagnostic use of PSA testing. We report evidence for such a reduction

in U.S. mortality rates through 1997. The decrease in prostate cancer mortality has occurred earlier than many had thought possible given the relatively slow growth rate of most prostate cancers and the associated long lead time (mean of 5.4 years)¹ for PSA. A close examination of stage-specific incidence and survival rates, however, reveals that, as Gann¹ conjectured, a rapid reduction in prostate cancer mortality is not inconsistent with a benefit of PSA testing and the variable behavior of prostate cancer.

Age-adjusted (1970 U.S. population as standard) prostate cancer mortality rates for black and white U.S. men 50 years of age or older are shown in the top two panels of Figure 1. The age-adjusted mortality rates for both white and black men rose after 1987 (an 11% increase for white men from 1987 through 1991 and a 14% increase for black men from 1987 through 1993). Similarly, an upturn in breast cancer mortality rates was noted during the period of rapid increase in the utilization of mammography.¹³ It is important to note, however, that mortality rates began to fall before incidence rates had peaked. The age-adjusted mortality rate for white men has decreased 16.1% since 1991, and the annual rate of decrease has accelerated steadily from 0.8% between 1991 and 1992 to 5.8% between 1996 and 1997. The age-adjusted mortality rate for black men has decreased 10.9% since 1993.

Subsequent discussion will be restricted to rates for white men, because of much greater variability of some rates (particularly stage-specific incidence rates and survival rates) for black men. Age-specific mortality rates for white men are shown in the lower five panels of

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U.S. Prostate Cancer Mortality Rates - 1950-97

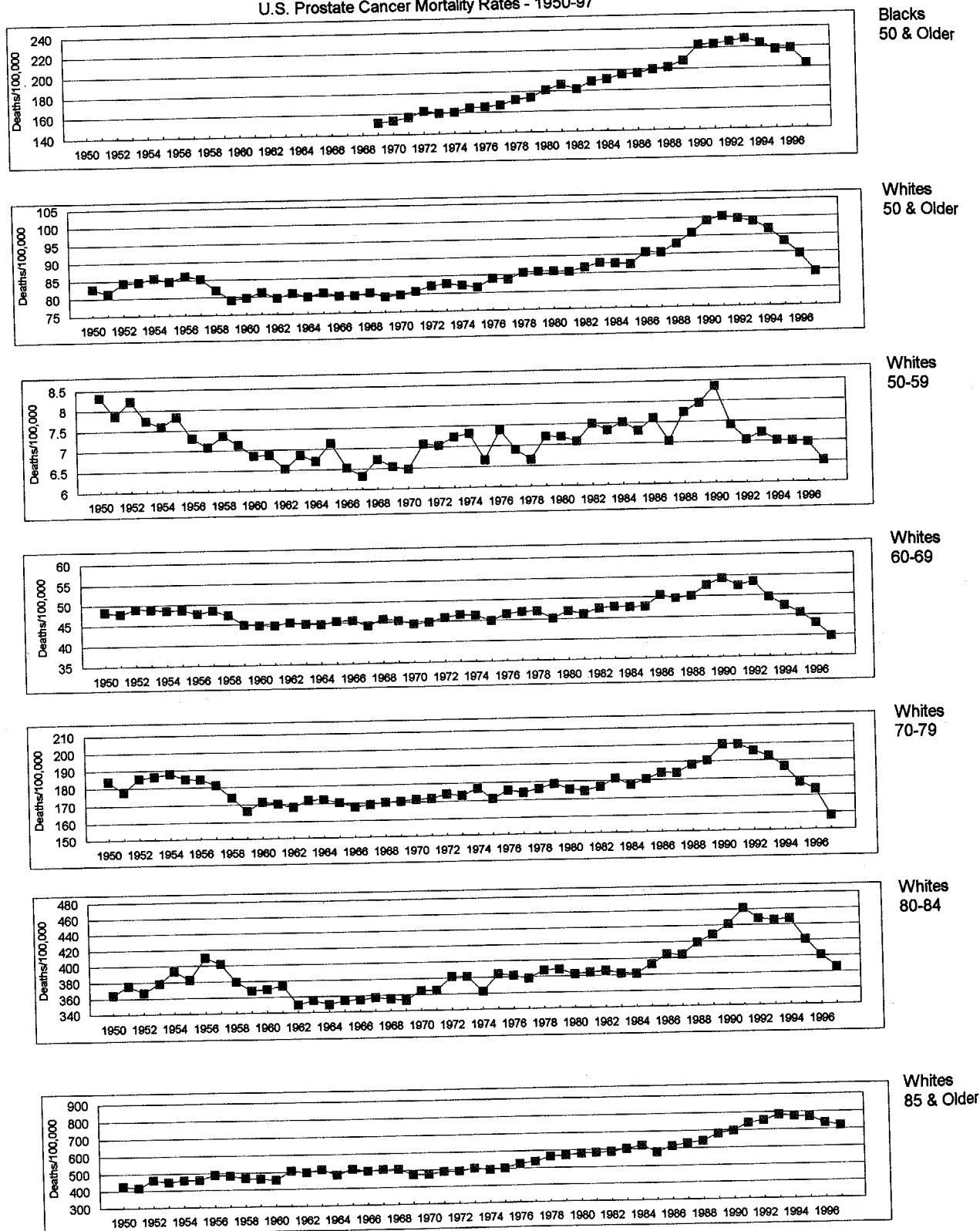


FIGURE 1. U.S. age-adjusted prostate cancer mortality rates (per 100,000 men), directly standardized using the 1970 U.S. standard million population. The y-axis for each panel has a different scale.

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Figure 1. The 1997 prostate cancer mortality rates in men both 60–69 years of age and 70–79 years of age were lower than they had been at any time since 1950. The 1997 mortality rate for men 50–59 years of age was the lowest it had been since 1970. For men 80–84 years of age, the 1997 mortality rate was lower than it had been since 1984. In fact, for all age groups between the ages of 50 and 84, both the 1996 and the 1997 prostate cancer mortality rates were lower than they had been at any time since 1986. Declines in mortality rates to such low levels, even though incidence rates remain far higher than pre-PSA testing incidence rates, would be expected if there is a benefit due to the early detection of prostate cancer using PSA testing.¹

Although a slight acceleration in diagnoses of prostate cancer was evident in 1987, marked increases in prostate cancer incidence rates due to PSA testing began in 1990. Mortality rates began decreasing in 1992, only 2 years after the marked increases in incidence began and 1 year after distant disease rates began to decline. Because rates for local and regional prostate cancer were still increasing when distant disease rates began to fall, the decrease in distant disease almost certainly reflects the stage shift expected from a beneficial screening procedure.¹¹ Distant disease rates through 1991 were unaffected by the increased use of PSA testing, and thus the sustained decrease in distant disease after 1992 cannot be explained by the reduced use of PSA testing. As noted by Gann,¹ prostate cancer must pass through the distant stage before becoming fatal. The extent to which stage is a determinant of prognosis is indicated by the prostate cancer relative survival rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.¹⁴ For prostate cancer cases diagnosed after 1987, the 1-, 3-, and 5-year relative survival rates for distant disease were 80%, 49%, and 33%, respectively. The same relative survival rates for patients with regional disease were 100%, 100%, and 98%, respectively. As an aside, it seems unlikely that the diagnosis of regional prostate cancer would have no impact whatsoever on a man's probability of surviving another 3 years; the 100% 3-year relative survival rate may reflect the fact that men who receive the best health care, and who thus are at lower risk of dying from most causes, are overrepresented among prostate cancer diagnoses because of increased access to PSA testing. In any event, the dramatic differences between regional disease and distant disease survival rates make it clear that a screening program that is able to detect a significant number of prostate cancers before they metastasize could have a relatively rapid impact on mortality.

The marked increase in moderately differentiated disease from 1987 through 1992 has been noted as evidence that PSA testing detects clinically significant disease, but PSA testing also led to a dramatic increase in diagnoses of poorly differentiated and undifferentiated disease. In particular, the rate in men 50 years of age and older of poorly differentiated or undifferentiated prostate cancer diagnosed in the regional stage increased from 20.8 per 100,000 men in 1987 to 46.2 per 100,000 in

1992 (as with all grades of prostate cancer, the rate of poorly differentiated and undifferentiated cancer has decreased with the reduced use of PSA testing since 1992). For cases diagnosed after 1987, the 1-, 3-, and 5-year SEER relative survival rates for these high-grade regional cancers were 100%, 96%, and 87%, respectively. Thus, survival rates for patients with even the highest-grade regional cancers are dramatically higher than survival rates, both short term and long term, for patients with distant cancers. To paraphrase Gann,¹ it is not hard to believe that among the thousands of such cases detected early by PSA testing, enough lives were saved to have a rapid impact on mortality rates.

Certain aspects of trends in men 50–59 years of age and men 85 years of age and older warrant further examination. The initial decrease in mortality rates after 1990 was of greater magnitude in men 50–59 years of age than in older men, despite lower utilization of PSA testing in this age group.¹⁵ Distant disease incidence rates in men 50–59 years of age began declining in 1988, at least 3 years before similar declines in older men (data not shown). Age-period-cohort analyses indicate a decreasing trend in birth cohort risk for men born from 1925 through 1945 (data not shown), indicating that favorable trends in risk factors may have contributed to recent mortality declines in men 50–59 years of age. Mortality rates in men 85 years of age and older have not yet declined to pre-PSA testing levels, despite the fact that their distant disease rates have decreased by the same magnitude (*ie*, more than 60%) observed in younger men. From 1987 through 1993, the percentages of prostate cancer deaths occurring in men with distant disease at diagnosis by age were: 54% for ages 50–59, 45% for ages 60–69, 35% for ages 70–79, 32% for ages 80–84, and 26% for ages 85 and older. These percentages decrease steadily with age, and thus the mortality benefit of the stage shift due to PSA testing (*ie*, reduction in the distant disease incidence rate) diminishes with age. The increasing percentage of deaths in lower-stage cases may result from an inability to treat such cases as aggressively in older men.

Other medical developments, such as the increased use of prostatectomies due to marked improvements in surgical methods and improved early detection due to the development of transrectal ultrasound, have also contributed to the improved survival of prostate cancer patients.⁸ Furthermore, new hormonal approaches to therapy (for example, antiandrogenic agents) were introduced about the same time as diagnostic PSA testing, and such treatments may be contributing to the decrease in distant disease, and the corresponding decrease in mortality, by delaying disease progression.¹¹ Only a randomized trial can unequivocally determine what portion of the decrease in prostate cancer mortality rates is due to PSA testing. The above examination of incidence, survival, and mortality rates indicates that a rapid effect of PSA testing on prostate cancer mortality is possible. Incidence patterns for black men are similar to those for white men, although changes occur somewhat later.^{3,4,9,11} As the figure demonstrates, black men are also

benefiting from the prostate cancer mortality declines, with decreases again occurring later than those for white men. If the observed decreases in prostate cancer mortality rates are due primarily to early detection by PSA testing, then the benefits of PSA testing should appear rather early in the follow-up of randomized trials evaluating PSA testing.

Note Added in Proof

The preliminary 1998 prostate cancer death rate (based on a sample of more than 85% of 1998 deaths) reported by the Centers for Disease Control and Prevention shows that prostate cancer mortality continued to decline through 1998.¹⁶ The directly standardized prostate cancer death rate (relative to the 1940 U.S. population) was 5.4 per 100,000 men in 1998, compared with rates of 5.7 per 100,000 in 1997 and 6.1 per 100,000 in 1996 (preliminary and final death rates were the same in both 1996 and 1997).¹⁶

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